Mitochondrial Homeostasis in Neurodegeneration and Ageing

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Ageing is driven by the inexorable and stochastic accumulation of damage in biomolecules vital for proper cellular function. Although this process is fundamentally haphazard and uncontrollable, senescent decline and ageing is broadly influenced by genetic and extrinsic factors. Numerous gene mutations and treatments have been shown to extend the lifespan of diverse organisms ranging from the unicellular *Saccharomyces cerevisiae* to primates. It is becoming increasingly apparent that most such interventions ultimately interface with cellular stress response mechanisms, suggesting that longevity is intimately related to the ability of the organism to effectively cope with both intrinsic and extrinsic stress. Key determinants of this capacity are the molecular mechanisms that link ageing to main stress response pathways and mediate age-related changes in the effectiveness of the response to stress. How each pathway contributes to modulate the ageing process is not fully elucidated. A better understanding of the dynamics and reciprocal interplay between stress responses and ageing is critical for the development of novel therapeutic strategies that exploit endogenous stress combat pathways against age-associated pathologies.

Mitochondria, the indispensable and highly dynamic, energy-generating organelles in all eukaryotic cells, play essential roles in fundamental cellular processes. Neuronal cells depend, perhaps more than any other cell type, on proper mitochondrial function. Mitochondrial impairment is a major hallmark of several age-related neurodegenerative and other pathologies linked to ageing. Interestingly, accumulation of damaged mitochondria has been observed in post-mortem brain of Alzheimer's disease patients [1]. Mitophagy is a selective type of autophagy mediating elimination of damaged mitochondria, and the major degradation pathway, by which cells regulate mitochondrial number in response to their metabolic state [2]. Little is known about the role of mitophagy in the pathogenesis of neurodegenerative and other age-associated maladies such as Alzheimer's disease. Although disease-associated tau and amyloid β are known to deregulate mitochondrial function, it remains elusive whether they also directly influence the efficiency of mitophagy. To address this question, we developed an in vivo imaging system to monitor mitophagy in diverse cell types [3]. We demonstrated that neuronal mitophagy is impaired in animal models of neurodegeneration. Urolithin A- and nicotinamide mononucleotide-induced mitophagy ameliorates several pathological features of Alzheimer's disease, including cognitive

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defects. Mitophagy stimulation restores memory impairment through PINK-1-, PDR-1-, or DCT-1-dependent pathways. Our findings suggest that impaired removal of damaged mitochondria is a pivotal event in age-related pathologies and the pathogenesis of Alzheimer's disease, highlighting mitophagy as a potential therapeutic intervention.

References

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